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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,622	05/16/2006	Susanne Moira Brown	6947-75757-01	9395

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,622	BROWN ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7-17,19-28,33-36,42,44,45,47,90,91 and 95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7-17,19-28,33-36,42,44,45,47,90,91 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-24-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 24, 2008 has been entered.

Status of Claims

Currently, claims 1-3, 5, 7-17, 19-28, 33-36, 42, 44-45, 47, 90-91, and 95 are pending and under examination on the merits in the instant case.

Response to Arguments

Applicant's arguments with respect to claims 1-3, 5-17, 19-28, 33-36, 42, 44-45, 47, 90-91 have been considered but are moot in view of the new ground(s) of rejection. See below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5, 7-17, 19-28, 33-36, 42, 44-45, 47, 90-91, and 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims comprise a non-neurovirulent herpes simplex virus comprising a nucleic acid encoding an "antisense" to the squamous cell carcinoma related oncogene (asSCCRO), wherein the nucleic acid encodes a nucleotide sequence "complementary" to SEQ ID NO:1 or its "complement". As such, the claimed asSCCRO (antisense) nucleic acid is simultaneously claimed to encode either an antisense sequence (complementary sequence) or a sense sequence (complementary sequence of said complementary sequence). Therefore, the structure of the claimed asSCCRO is internally inconsistent and ambiguous, thereby rendering the claimed invention indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 7-17, 33-36, 42, 44-45, 47, 90-91, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Echeverri et al. (US 2004/0048277 A1, this US-PGPUB was previously published as WO 200238805 A2) in view of Rampling et al. (*Gene Therapy,* 2000, 7:859-866), Burton et al. (*DNA and Cell Biology,* 2002, 21:915-936), and Glorioso et al. (WO 98/51809, citation of record).

The claims are drawn to HSV1716 comprising an antisense nucleic acid that encodes the complementary sequence of SEQ ID NO:1, and methods of killing tumor cells *in vitro* and *in vivo* by administering said HSV1716 to a patient in need thereof.

The instant specification (see page 34) as well as the IDS filed on July 13, 2006 (see reference No. XP-002335921) teach that the polynucleotide sequence of SEQ ID NO:1 is synonymous with GenBank Accession No. AF456425, which encodes the protein sequence of GI:18700655 and that it is named "squamous cell carcinoma-related oncogene (SCRO) or (SCCRO)".

Echeverri et al. teach an isolated nucleic acid sequence of SEQ ID NO:12 comprising a human RP42 cDNA sequence that is identified as NCBI Accession No. AF292100. They teach that the human RP42 cDNA is functionally involved in cell division and proliferation. They teach that any homologues, orthologues, and derivatives of the human RP42 cDNA sequence are excellent tools for use in the development of a wide range of therapeutics including anti-proliferative agents for treatment of proliferative or neoplastic diseases. It is found that the nucleotide sequence of SEQ ID NO:12 comprises nucleotides 58-837 of SEQ ID NO:1 of the instant application. Furthermore, the GenBank database as directed by the disclosure of the

specification (page 34) reveals that RP42 is synonymous with SCRO or SCCRO and that the RP42 mRNA sequence is homologous to that of SCRO or SCCRO. Indeed, it is found that the RP42 mRNA sequence (AF292100) encodes the protein sequence of 291 amino acids identified as GI:9896486, wherein the 291 amino acids are identical to those of GI:18700655 encoded by SCCRO (AF456425). Echeverri et al. further teach that an antisense polynucleotide sequence of SEQ ID NO:12 inserted into a therapeutically usable viral vector is suitable for therapeutic purposes, especially for tumors and cancers. See paragraphs 0017-0034, 0041, 0054, 0058-0059, 0067-0068; claims 3-4. Echeverri et al. do not teach that said therapeutically usable viral vector is a non-neurovirulent herpes simplex virus.

Rampling et al. teach that non-neurovirulent herpes simplex virus, in particular, the ICP34.5 deleted HSV1716 strain, has been shown to be effective in slowing the tumor growth in living mammals including humans tested in preclinical settings. They teach that the use of HSV1716 in humans having cancer has shown to be effective and safe with no evidence of toxicity or adverse effects. They therefore suggest that the HSV1716 has therapeutic potential for treatment of cancer. See the entire reference.

Burton et al. teach that various types of HSV-1 vectors have been widely used as gene therapy vectors. They teach that genetic manipulation of the HSV-1 viral vectors is relatively straightforward, and one can introduce exogenous sequences into the vectors. They teach that HSV-1 viral vectors have been shown to be effective in expressing long-term transgene expression in various animal models of human disease. See the entire reference.

Glorioso et al. teach that a mutant HSV virus can be engineered by inserting a pharmacologically active therapeutic polynucleotide within the HSV genome via homologous recombination procedure (pages 3-5; Figures 1-2). They teach that the polynucleotide is a

synthetic DNA, cDNA, genomic DNA fragment, biologically active antisense RNA, or ribozyme (page 15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the anticancer agent HSV1776 with the anticancer agent nucleic acid that is complementary to SEQ ID NO:1 of the instant case in such a way that the antisense nucleic acid is inserted into the HSV1776.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because the mRNA sequence of SEQ ID NO:1 of the instant application was known to encode SCCRO or RP42, which plays a functional role in cell division and proliferation and therefore inhibiting its expression by antisense technology was known to be useful for anticancer therapeutics, as evidenced by the teachings of Echeverri et al. Furthermore, inserting an antisense polynucleotide sequence into a therapeutically suitable viral vector such as HSV was common, straightforward genetic engineering procedure as evidenced by the teachings of Echeverrie et al., Burton et al., and Glorioso et al. Hence, one of ordinary skill in the art wanting to use the antisense polynucleotide against SCCRO or RP42 would have been motivated to select a therapeutically usable HSV vector that is particularly usable for cancer treatment. Since the ICP34.5 deleted HSV1716 strain has been shown to be effective in slowing the tumor growth in living mammals including humans tested in preclinical settings, thereby showing therapeutic potential for cancer treatment as taught by Rampling et al., the skilled artisan desiring to utilize the antisense polynucleotide against SCCRO or RP42 for cancer treatment would have been motivated to use the ICP34.5 deleted HSV1716 strain, which has been shown to have anticancer effects in humans, as the carrier or vector of said antisense polynucleotide. The skilled artisan would have been also motivated to construct such recombinant virus, HSV1716 carrying

an antisense polynucleotide sequence against SCCRO or RP42, in order to increase the anticancer effect of HSV1716 or the antisense polynucleotide by combining them in a single composition.

See also *In re Kerkhoven*, wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Since both the antisense polynucleotide targeted against the gene encoding RP42 (or SCCRO) and the HSV1716 vector were recognized in the art as anticancer therapeutics agents, it would have been *prima facie* obvious to combine them for treatment of cancer with a reasonable expectation of success. See also MPEP 2144.06.

Furthermore, the protein produced by the claimed sequence of SEQ ID NO:1 encoding SCCRO is identical to that produced by SEQ ID NO:12 encoding RP42 of Echeverri et al. Hence, the antisense polynucleotide complementary to SEQ ID NO:12 of Echeverri et al. will inherently confer the functional property of inhibiting or slowing squamous tumor cell growth.

Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 1-3, 5, 7-17, 19-28, 33-36, 42, 44-45, 47, 90-91, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Echeverri et al., Rampling et al., Burton et al., and

Glorioso et al. as applied to claims 1-3, 5, 7-17, 33-36, 42, 44-45, 47, 90-91, and 95 above, and further in view of Jacobs et al. (*Human Gene Therapy,* 2003, 14:277-297, also citation of record).

The claims are drawn to HSV1716 comprising an antisense nucleic acid that encodes the complementary sequence of SEQ ID NO:1, an IRES, a GFP/EGFP sequence, a SV40 polyadenylation sequence, and methods of killing tumor cells *in vitro* and *in vivo* by administering said HSV1716 to a patient in need thereof.

The combined references of Echeverri et al., Rampling et al., Burton et al., and Glorioso et al. teach a recombinant HSV1716 containing an antisense polynucleotide sequence against SCCRO or RP42, which is useful for cancer treatment. They do not teach that the recombinant HSV1716 further comprises other functional elements, such as the claimed IRES, GFP/EGFP, and SV40 sequences.

Jacobs et al. teach genetically engineered HSV-1 vectors containing IRES, GFP/EGFP, and SV40 sequences. They teach that such HSV-1 vectors further containing any therapeutic gene will provide an indirect, noninvasive assessment of the distribution of the therapeutic gene expression by fluorescent detection. They further teach that such HSV-1 vectors carrying a therapeutic gene is effective in slowing tumor growth in mice *in vivo*. They also teach guidelines as to how to construct such fusion, recombinant, genetically engineered HSV-1 vectors, which represent a "proof-of-principle" vector system for gene therapy combined with imaging or monitoring of vector-mediated gene transduction. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a recombinant HSV1716 containing an antisense polynucleotide sequence against SCCRO or RP42, further comprising IRES, GFP/EGFP, and SV40 sequences.

With the "proof-of-principle" vector system for gene therapy in conjunction with tumor progress monitoring as taught by Jacobs et al., one of ordinary skill in the art would have recognized the utility of constructing the claimed recombinant vector (e.g., monitoring of tumor growth), and therefore would have been motivated to make the claimed recombinant HSV1716 further containing IRES, GFP/EGFP, and SV40 sequences. Since the methodology as well as skills required to construct the claimed recombinant vector were available in the art at the time the invention was made and within the technical grasp of one of ordinary skill in the art, the skilled artisan would have had a reasonable expectation of success in arriving at the claimed invention. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 1-3, 5, 7-17, 33-36, 42, 44-45, 47, 90-91, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lodes (WO 200052165 A2) in view of Rampling et al. (*Gene Therapy,* 2000, 7:859-866), Burton et al. (*DNA and Cell Biology,* 2002, 21:915-936), and Glorioso et al. (WO 98/51809, citation of record).

The claims are drawn to a HSV1716 comprising an antisense polynucleotide complementary to a fragment of SEQ ID NO:1 and methods of killing tumor cells *in vitro* and *in vivo* by administering said HSV1716 to a patient in need thereof.

The instant specification teaches that the "fragment" recited in (iii) of claims 1, 5, and 8 comprises at least 20 nucleotides. See page 8, which states, "The fragment referred to at (iii) may comprise at least 20 nucleotides and may be limited to no more than 900 nucleotides." Furthermore, claim 7 recites that said "fragment" is at least 20 nucleotides.

Lodes teaches a polynucleotide sequence of SEQ ID NO:91, which corresponds to nucleotides 53-492 of SEQ ID NO:1 of the instant application. Lodes teaches that a composition comprising an antisense polynucleotide of SEQ ID NO:91 and a pharmaceutically acceptable carrier is useful to treat breast cancer. See pages 2-3, 13-14; claims 11, 19. Lodes teaches that the antisense polynucleotide sequence can be incorporated into a viral vector to permit entry into a cell of a mammal, particularly for therapeutic purposes. Lodes teaches that techniques for incorporating DNA into a viral vector is well known to those of ordinary skill in the art (page 15). Lodes does not teach that said viral vector is a non-neurovirulent herpes simplex virus.

Rampling et al. teach that non-neurovirulent herpes simplex virus, in particular, the ICP34.5 deleted HSV1716 strain, has been shown to be effective in slowing the tumor growth in living mammals including humans tested in preclinical settings. They teach that the use of HSV1716 in humans having cancer has shown to be effective and safe with no evidence of toxicity or adverse effects. They therefore suggest that the HSV1716 has therapeutic potential for treatment of cancer. See the entire reference.

Burton et al. teach that various types of HSV-1 vectors have been widely used as gene therapy vectors. They teach that genetic manipulation of the HSV-1 viral vectors is relatively straightforward, exploiting the recominogenic properties of HSV-1 to introduce exogenous sequences by homologous recombination. They teach that HSV-1 viral vectors have been shown to be effective in expressing long-term transgene expression in various animal models of human disease. See the entire reference.

Glorioso et al. teach that a mutant HSV virus can be engineered by inserting a pharmacologically active therapeutic polynucleotide within the HSV genome via homologous recombination procedure (pages 3-5; Figures 1-2). They teach that the polynucleotide is a

synthetic DNA, cDNA, genomic DNA fragment, biologically active antisense RNA, or ribozyme (page 15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the anticancer agent HSV1776 with the anticancer agent nucleic acid that is complementary to a fragment of SEQ ID NO:1 of the instant case in such a way that the antisense nucleic acid is inserted into the HSV1776.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because the antisense fragment of SEQ ID NO:1 of the instant application was known to be useful for anticancer therapeutics, as evidenced by the teachings of Lodes. Furthermore, inserting an antisense polynucleotide sequence into a therapeutically suitable viral vector such as HSV was common, straightforward genetic engineering procedure as evidenced by the teachings of Lodes, Burton et al., and Glorioso et al. Hence, one of ordinary skill in the art wanting to use the antisense fragment of SEQ ID NO:1 would have been motivated to select a therapeutically usable HSV vector that is particularly usable for cancer treatment. Since the ICP34.5 deleted HSV1716 strain has been shown to be effective in slowing the tumor growth in living mammals including humans tested in preclinical settings, thereby showing therapeutic potential for cancer treatment as taught by Rampling et al., the skilled artisan desiring to utilize the antisense fragment of SEQ ID NO:1 for cancer treatment would have been motivated to use the ICP34.5 deleted HSV1716 strain, which has been shown to have anticancer effects in humans, as the carrier or vector of said antisense polynucleotide. The skilled artisan would have been also motivated to construct such recombinant virus, HSV1716 carrying an antisense fragment of SEQ ID NO:1, for additive anticancer effect of HSV1716 or the antisense fragment of SEQ ID NO:1 by combining them in a single composition.

Further, since both the antisense polynucleotide targeted against SEQ ID NO:91 of Lodes and the HSV1716 of Rampling et al. were recognized in the art as anticancer therapeutic agents, it would have been prima facie obvious to combine them for treatment of cancer with a reasonable expectation of success. See *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) and MPEP 2144.06.

Furthermore, since the antisense polynucleotide of Lodes meets the structural requirement set forth in claim 1, it will inherently confer the functional property of inhibiting or slowing squamous tumor cell growth, absent evidence to the contrary.

Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 1-3, 5, 7-17, 19-28, 33-36, 42, 44-45, 47, 90-91, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lodes, Rampling et al., Burton et al., and Glorioso et al. as applied to claims 1-3, 5, 7-17, 33-36, 42, 44-45, 47, 90-91, and 95 above, and further in view of Jacobs et al. (*Human Gene Therapy,* 2003, 14:277-297, also citation of record).

The claims are drawn to HSV1716 comprising an antisense nucleic acid that encodes the complementary sequence of SEQ ID NO:1, an IRES, a GFP/EGFP sequence, a SV40 polyadenylation sequence, and methods of killing tumor cells *in vitro* and *in vivo* by administering said HSV1716 to a patient in need thereof.

The combined references of Lodes, Rampling et al., Burton et al., and Glorioso et al. teach a recombinant HSV1716 containing an antisense fragment of SEQ ID NO:1, which is

useful for cancer treatment. They do not teach that the recombinant HSV1716 further comprises other functional elements, such as the claimed IRES, GFP/EGFP, and SV40 sequences.

Jacobs et al. teach genetically engineered HSV-1 vectors containing IRES, GFP/EGFP, and SV40 sequences. They teach that such HSV-1 vectors further containing any therapeutic gene will provide an indirect, noninvasive assessment of the distribution of the therapeutic gene expression by fluorescent detection. They further teach that such HSV-1 vectors carrying a therapeutic gene is effective in slowing tumor growth in mice *in vivo*. They also teach guidelines as to how to construct such fusion, recombinant, genetically engineered HSV-1 vectors, which represent a "proof-of-principle" vector system for gene therapy combined with imaging or monitoring of vector-mediated gene transduction. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a recombinant HSV1716 containing an antisense fragment of SEQ ID NO:1, further comprising IRES, GFP/EGFP, and SV40 sequences.

With the "proof-of-principle" vector system for gene therapy in conjunction with tumor progress monitoring as taught by Jacobs et al., one of ordinary skill in the art would have recognized the utility of constructing the claimed recombinant vector (e.g., monitoring of tumor growth), and therefore would have been motivated to make the claimed recombinant HSV1716 further containing IRES, GFP/EGFP, and SV40 sequences. Since the methodology as well as skills required to construct the claimed recombinant vector were available in the art at the time the invention was made and within the technical grasp of one of ordinary skill in the art, the skilled artisan would have had a reasonable expectation of success in arriving at the claimed invention. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 1-3, 5, 7-17, 19-28, 33-36, 42, 44-45, 47, 90-91, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Estilo et al. (*Clinical Cancer Research,* 2003, 9:2300-2306, citation of record) in view of Rampling et al. (*Gene Therapy,* 2000, 7:859-866), Crooke (*Oncogene,* 2000, 19:6651-6659), and Jacobs et al. (*Human Gene Therapy,* 2003, 14:277-297, also citation of record).

The claims are drawn to HSV1716 comprising an antisense polynucleotide against SCCRO, an IRES, a GFP/EGFP sequence, a SV40 polyadenylation sequence, and methods of killing tumor cells *in vitro* and *in vivo* by administering said HSV1716 to a patient in need thereof.

Estilo et al. teach that the mRNA expression level of SCCRO is significantly overexpressed in malignant head and neck squamous cell carcinoma tissues. They expressly report that SCCRO may "provide a basis for the development of novel anti-tumor strategies." See the last sentence on page 2305. Estilo et al. do not teach that the development of said novel anti-tumor strategies include HSV1716 carrying the anti-SCCRO nucleic acid sequence, further comprising IRES, GFP/EGFP and SV40 polyadenylation sequences.

Rampling et al. teach that non-neurovirulent herpes simplex virus, in particular, the ICP34.5 deleted HSV1716 strain, has been shown to be effective in slowing the tumor growth in living mammals including humans tested in preclinical settings. They teach that the use of HSV1716 in humans having cancer has shown to be effective and safe with no evidence of toxicity or adverse effects. They therefore suggest that the HSV1716 has therapeutic potential for treatment of cancer. See the entire reference.

Crooke teaches that antisense technology is the most advanced nucleic acid-based gene therapy, especially for cancer treatment. He reports that a number of antisense drugs have undergone clinical trials for various cancer treatment regimes, and therefore, he teaches that antisense drugs have potential roles in anticancer therapy. He also teaches that the antisense drugs can be used in combination with traditional cytotoxic drugs for even more anticancer benefits. See the entire reference.

Jacobs et al. teach genetically engineered HSV-1 vectors containing IRES, GFP/EGFP, and SV40 sequences. They teach that such HSV-1 vectors further containing any therapeutic gene will provide an indirect, noninvasive assessment of the distribution of the therapeutic gene expression by fluorescent detection. They further teach that such HSV-1 vectors carrying a therapeutic gene is effective in slowing tumor growth in mice *in vivo*. They also teach guidelines as to how to construct such fusion, recombinant, genetically engineered HSV-1 vectors, which represent a "proof-of-principle" vector system for gene therapy combined with imaging or monitoring of vector-mediated gene transduction. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an antisense drug against SCCRO and combine it with HSV1716 of Rampling et al. as a single recombinant composition for treatment of head and neck squamous carcinoma, by combining the teachings of the prior art references cited herein.

One of ordinary skill in the art would have been motivated to do so because Estilo et al. expressly taught that SCCRO can be used in anti-cancer therapeutics, because Rampling et al. taught HSV1716 can be used in anti-cancer therapeutics, and because Crooke taught that antisense technology is the most promising gene therapy strategy and that combining antisense drugs with known anti-tumor agents provides greater beneficial anticancer effects. Since

employing antisense technology for a gene known to be involved in tumorigenesis was routine procedure for potential anticancer strategies as taught by Crooke, and since additive effects of combining antisense drugs with known anticancer agents were also taught by Crooke, one of ordinary skill in the art would have been motivated to combine the art-recognized antisense agent HSV1716 with the antisense drug targeted to SCCRO. Since methodologies for making antisense drugs against a known gene as well as making a recombinant herpes simplex virus comprising an anticancer therapeutic gene, IRES, GFP/EGFP, and SV40 sequences were known and the skills required to produce the claimed recombinant product were within the technical grasp of an ordinary skilled artisan at the time of the invention, as evidenced by Crooke and Jacobs et al., one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention at the time of the invention. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635